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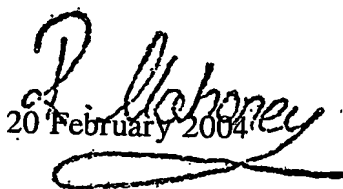
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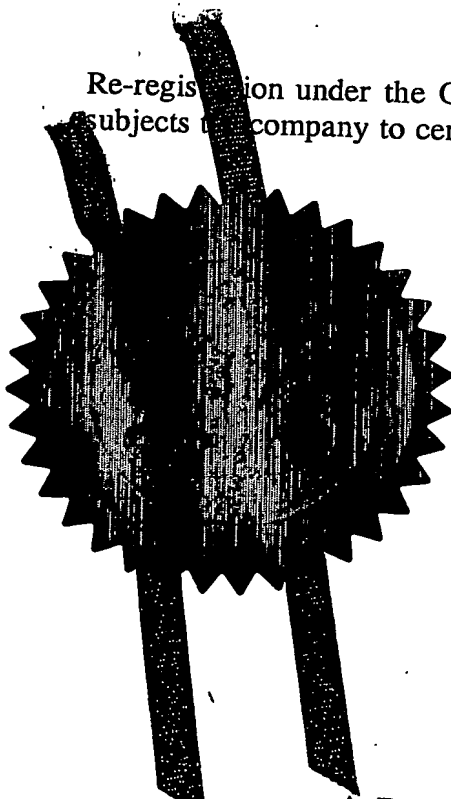
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3 Full name, address and postcode of the or of each applicant (underline all surnames)

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Patents ADP number (if you know it)

8559924001

If the applicant is a corporate body, give the country/state of its incorporation

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4. Title of the invention **TRANSDERMAL GRANISETRON**

5. Name of your agent (if you have one)
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

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TRANSDERMAL GRANISETRON

DEP-1000

The present invention relates to transdermal patches comprising granisetron, to uses therefor and to methods for their preparation.

Nausea and vomiting are frequently the most debilitating and discouraging symptoms of medications administered to cancer patients. The side effects of emesis are not just unpleasant because of the condition, *per se*, they can lead to serious dehydration and even malnutrition.

Patients on regimens of anti-cancer drugs that have high associated emetogenic potential (e.g. cisplatin, streptozotocin, carmustine, procarbazine, mechlorethamine and dactinomycin) are particularly affected and, therefore, particularly benefit from aggressive, concomitant administration of antiemetic drugs to curb intractable nausea and vomiting. Other patient groups that benefit from such treatment regimens are those suffering from post-operative nausea and vomiting.

Cytotoxic chemotherapy is thought to release serotonin from certain cells of the small intestine. The released serotonin may stimulate the vagal afferent nerves through the 5-HT₃ (5-hydroxytryptamine₃) receptors, thus stimulating the vomiting reflex. Accordingly, it is assumed that 5-HT₃ receptor antagonistic drugs, such as ondansetron, granisetron and tropisetron, exert their effects by blocking serotonin, both peripherally, on vagal nerve terminals, and centrally, in the chemo-receptor trigger zone.

5-HT₃ receptor antagonistic antiemetics are currently administered intravenously, orally, or rectally. Intravenous administration can only be performed under medical supervision and causes significant patient discomfort, such as redness and burning, at the injection site. Problems are compounded in paediatric medicine, owing to children's dislike of needles, and there are always concerns regarding needle-stick injuries. Oral administration has disadvantages associated with its frequency (up to four times daily), as well as the issues resulting from utilisation of such a route of delivery in a patient suffering severe nausea and vomiting and patients suffering from head and neck cancer can often not swallow properly. The pulsatile

nature of oral delivery may also cause problems resulting from deviations from the therapeutic window (often responsible for side effects). Rectal delivery circumvents, to some extent only, the pulsatile nature of oral delivery and is not the most convenient, nor widely acceptable, approach to drug delivery.

Hence, there is a need for a non-oral drug delivery system capable of maintaining constant plasma levels of antiemetic agents over extended periods of time. Indeed, there are other indications for 5-HT₃ receptor antagonists that cannot currently be fully exploited, and that would benefit from more controlled delivery than that currently available.

The 5-HT₃ receptors are located primarily in peripheral and central neurons, and appear to be involved in the depolarisation of peripheral neurons, pain, and the emesis reflex. Thus, other indications include migraine, anxiety, and cognitive and psychotic disorders, and, more specifically, the treatment or prevention of depression, schizophrenia, psychosis in postnatal depression, fibromyalgic pain, irritable bowel syndrome, alcoholism, obstructive sleep disturbed breathing, motion sickness, loss of cognitive function, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation and eating disorders, such as bulimia.

Transdermal delivery of drugs through the skin is a recognised method for maintaining relatively steady plasma levels of therapeutic agents whilst also circumventing the pain, discomfort and inconvenience of intravenous, oral and rectal drug delivery. Hence, post-chemotherapy and post-operative transdermal anti-emetogenic therapy has the potential to ease the suffering of patients who are not only experiencing nausea and vomiting, resulting from their primary therapy, but also suffering significant discomfort associated with their medical condition *per se*.

Various attempts have been made to provide successful, transdermal administration of 5-HT₃ receptor antagonists. However, the majority of patent publications on the subject simply includes the option of transdermal delivery, as one option among many, as a possible route of administration.

Similarly, various patent publications relating to specific transdermal or iontophoretic devices cite ondansetron, amongst others, for possible inclusion in these devices. US-A-5,372,819 (Minnesota Mining and Manufacturing Company) cites, amongst a large number of other compounds of numerous classes, metoclopramide and ondansetron as antiemetics for inclusion in a transdermal patch. However, there are no specific examples for any of the drugs cited that demonstrate the therapeutic potential of the device, nor which address the issues concerning the transdermal delivery of these compounds. Similarly, WO 94/07468 (Cygnus Inc.) cites granisetron and ondansetron as exemplary antiemetics in a less extensive list of compounds for inclusion in another transdermal device.

Japanese laid-open no. 8-34731 discloses percutaneous preparations of granisetron, using such formulation forms as creams, liniments, lotions, gels, tapes and patches. These formulations comprise a vehicle and a permeation enhancer, which may be selected from alcohols, fatty acids, esters of these, and others. The Examples of this publication use the skin of the hairless mouse to establish likely flux in humans. Despite the skin of these animals having about 10 fold greater permeability than human skin, it was still necessary to employ a 100 cm² patch. An object of the present invention is to reduce the size of patch necessary to achieve antiemetic blood plasma levels of drug.

Ondansetron is a widely used 5HT₃ antagonist. Owing to the systemic nature of the antiemetic effect, relatively high therapeutic plasma levels of ondansetron are required to achieve efficacy. Hence, the successful transdermal delivery of a therapeutically effective amount of ondansetron requires that the transdermal device provide a relatively high flux of the drug across the skin. Such high fluxes can only be maintained over a clinically relevant time period if the drug loading within the patch is great enough to ensure that drug depletion does not reduce delivery rate with time, *i.e.* a high flux is sustained.

High drug loading in transdermal patches is generally achieved by the use of so-called 'reservoir patches'. Reservoir patches contain solutions of drug that allow higher loadings than can normally be achieved in the alternative matrix patch technology. These high drug loadings are achieved by the use of relatively high

volumes of solvents, such as ethanol or propylene glycol, which are often irritating to the skin. By virtue of the volume of their contents, reservoir patches are normally physically and visually bulky and, once applied, are not flush with the skin surface. Such attributes make them cosmetically unacceptable to many patients.

Furthermore, adherence of reservoir patches to the skin can be sub-optimal, as the adhesive is only positioned around only the periphery of the patch, which is intended to allow the drug to permeate from the central reservoir across a rate controlling membrane in contact with the skin.

By way of contrast, matrix patches have the ability to adhere to the skin much more effectively, owing to the fact that the area of adhesive in contact with the skin is coterminous with the total, effective area of the patch, thereby also securing a maximal secure interface between patch and skin. This has implications for the effective utilisation of the skin as a route of drug delivery, as well as simply ensuring that the patch remains in place.

However, the very nature of a matrix patch sets a limit on the amount of active material that can be carried by the patch, as reservoir for the drug is provided by the adhesive matrix, rather than separately. Matrix patches simply are not suitable for drugs that need to be administered in high amounts, such as ondansetron, as they cannot carry sufficient drug. For example, WO 00/47208 (Sam Yang Corporation) and EP-A-1,064,939 (Novosis Pharma AG) disclose transdermal ondansetron reservoir patches, while WO 00/47208 specifically excludes matrix patches on the grounds that the obtainable drug loading is insufficient.

WO98/53815, to 3M, discloses compositions comprising tropisetron or granisetron in acrylic adhesives, and that are suitable for transdermal administration. However, adhesives containing nucleophilic, such as hydroxyl, moieties are taught against, as it is demonstrated that tropisetron is unstable in their presence. The authors speculate that this instability may be caused by increased cross-linking within the adhesive that may also involve binding of the drug to the polymer, and that the basic nature of the drugs may catalyse this process. Such reactions may involve the

production of undesirable drug degradation products and any drug/polymer binding could be expected to reduce flux.

However, we have now found that, while adhesives comprising electronegative groups, such as COOH groups, cannot be used in the manufacture of effective transdermal patches, adhesives comprising hydroxyl groups are significantly better than non-nucleophilic, electroneutral adhesives, and that such adhesives substantially enhance flux of granisetron, for example.

Thus, in a first aspect, the present invention provides an adhesive patch suitable for the transdermal administration of granisetron, wherein the adhesive is an acrylic adhesive containing non-acidic hydroxyl moieties.

It is preferred that the non-acidic hydroxyl moieties, or OH groups as they are also referred to herein, are provided by the simple expedient of incorporating the appropriate monomers during manufacture of the adhesive polymer. Suitable monomers may include the acrylates and methacrylates substituted in any desired manner. Particularly preferred acrylates are the hydroxymethyl, hydroxyethyl and hydroxypropyl acrylates, especially hydroxyethylacrylate (HEA). Preferred methacrylates are the hydroxymethyl and hydroxyethyl methacrylates.

Hydroxyl groups of the adhesives of the present invention are preferably not associated with any other polar moiety, or part of any other group. In particular, it is preferred that the OH group not be part of any COOH, NCOH and the like groups. While minimal levels of such groups may be tolerated, it is preferred that adhesives of the present invention have substantially no detectable levels of such groups.

Adhesives of the present invention are preferably pressure sensitive. Acrylic pressure sensitive adhesives are generally made with a substantial amount of a primary acrylate monomer which, in most commercial acrylic adhesives, is limited to either 2-ethylhexyl acrylate or butyl acrylate. Other monomers may be suitable, provided that they have a sufficiently low glass transition temperature (T_g).

Modifying monomers are also commonly used, and may be selected from virtually any vinyl monomer. The modifying comonomers may be selected from those having a modifying effect on tack, such as vinyl acetate and styrene in polyacrylates, and vinyl pyrrolidone and acrylonitrile in polymethacrylates, to comonomers containing functional groups, which can include those mentioned above where it is desired to incorporate an OH group.

Typical levels of primary monomer are between 50 and 98% by weight, and the modifying monomer, such as vinyl acetate, styrene or methacrylonitrile, is typically present in an amount of about 10 to 40% w/w. The functionality, or hydroxyl, comonomer is preferably present in an amount of from 0.5 to 20% w/w, preferably between 3 and 10% w/w by weight of total monomers.

The adhesive patches of the present invention are effective without having to incorporate any plasticisers or permeation enhancers, such as isopropyl myristate (IPM). This is advantageous, as it reduces the number of constituents, and excludes a possible source of irritation, as well as excluding a substance that reduce the cohesion of the adhesive. Permeation enhancers are generally required in transdermal patches. However, in the patches of the present invention, the presence of the polar residues has a surprising effect on the transdermal flux, increasing permeation to a level where substantially the whole load can be dispensed in a 24 hour period, if desired.

Indeed, any form of chemical interaction with the adhesive would normally be expected only to hamper flux and transdermal penetration by retarding release. In the accompanying examples, we demonstrate that the presence of hydroxyl groups in the adhesive actually substantially facilitates release, compared with release from directly comparable adhesives with no polar groups. It is particularly surprising that initial release levels are several orders of magnitude higher than from non-nucleophilic adhesives, and enables transdermal patches made with an adhesive of the invention to be used in circumstances requiring effective levels of granisetron within a matter of hours.

The patches of the present invention also have the ability to dispense the granisetron in a substantially uneven form, but in a manner ideal for the treatment of

chemically induced emesis. Such emesis can be divided into acute and delayed, with the acute emesis resulting from the chemotherapy and high levels of anti-neoplastic drug, and the delayed form being a longer term response. The acute reaction necessitates higher levels of antiemetic over a period of about 12 hours from administration, while the delayed form needs a lower level over subsequent days. The patches of the present invention can be employed to provide this sort of regimen and, if used individually, will generally tend to provide such a regimen.

In single dose chemotherapy, 5HT₃ antagonists are commonly used for the prevention of acute nausea and vomiting associated with the administration of emetogenic chemotherapy. Although the efficacy of these agents in the acute setting is clear, the most appropriate dose and the relationship between efficacy and plasma levels are not. Published studies also clearly demonstrate the efficacy of 5HT₃ antagonists (administered with dexamethasone) in delayed emesis (Guillem *et al.*, 1998; Friedman *et al.*, 2000) but again do not address issues of dose response.

Despite the lack of information regarding their therapeutic relevance, plasma profiles are still a useful marker in demonstrating bioequivalence when switching dosage form. Most dosage forms (injections, tablets and oral syrups) of the 5HT₃ antagonists result in plasma profiles typical of pulsatile drug delivery *i.e.* short T_{max} values and relatively high C_{max} values followed by decreases in plasma levels concomitant with drug half life.

The most common granisetron regimen in chemotherapy is an initial dose of 1 or 2 mg prior to treatment for the prevention of acute emesis, followed by a 2 mg daily dose for 3 to 5 days in combination with dexamethasone, for the prevention of delayed emesis. Continual twice daily dosing of 1 mg in cancer patients (Physicians Desk Reference, 2001) yields average peak plasma levels of 6 ng/ml and a clearance value of 0.52 L/hr/kg. For a 60 kg patient these data indicate that a flux of about 190 µg/h from a transdermal patch would be sufficient to maintain plasma levels of 6 ng/ml. However, maintenance of plasma levels at these C_{max} values is not required for efficacy in delayed emesis (Cupissol *et al.*, 1993) and the minimum required therapeutic plasma level in acute emesis is not known.

The minimum therapeutic plasma level required for efficacious use of any drug is ideally assessed by titrated, prolonged IV infusion studies coupled to clinical response in patients. Continual IV infusion of granisetron at a rate of only 40 µg/h has been shown (Kalaycio *et al.*, 1998) to alleviate delayed emesis in cancer patients, suggesting that maintenance of a lower plasma level (approximately 1.5 ng/ml) may be more appropriate in this respect.

The main limitation of a patch in this setting is the delay in achieving plasma levels appropriate for efficacy. Whilst T_{\max} values associated with oral granisetron are approximately 2 hours, those associated with its transdermal administration are generally longer. However, levels associated with the patches of the present invention are already effective after about 2 hours, and rising, thereby making patches of the invention surprisingly useful in the treatment of acute emesis.

Where it is desired to provide a continuous high level of granisetron, then patches may be applied twice a day, for example, or as often as indicated by the skilled physician.

Levels of granisetron may be up to about 10% by weight although, in DuroTak 387-2287, an adhesive provided by National Starch, 8% w/w is generally higher than preferred, as crystallisation can occur. Thus, in preferred adhesives of the invention, levels of granisetron are below 8% w/w. It is preferred to provide levels of granisetron above 4%, and preferably above 5% w/w. It is particularly preferred to provide levels between 6% and 7.7% w/w. In preferred adhesive, no crystallisation was observed in patches containing up to 7.7% after one month. The concentration of granisetron in the patch is between 6 and 8%, but is subject to such considerations as age and weight of the patient, as well as physical condition and other concomitant treatments or therapies, suitable levels of granisetron being readily determined by the skilled physician.

It is generally preferred to avoid crystallisation of granisetron in the patches of the present invention, owing to cost considerations. However, crystallisation readily affords a reservoir of drug, which can dissolve into the patch and then be dispensed to the patient, once the patch has been depleted, at least partially, of the initial levels of

granisetron. Where a patch is intended for immediate rapid delivery, for example, then crystallisation provides no advantage, and adds to production costs.

It is also an advantage of the present invention that flux from the patch is so great that small patches are readily employed to substantial effect, and that large patches, such as those disclosed in WO98/53815, are not generally necessary, unless very large fluxes are required, for example.

Polar groups in the polymer chains of adhesives have the added benefit of increasing skin adhesion. The inclusion of such groups also increases formulation options as it allows cross-linking of the adhesives to be achieved if required, thereby improving cohesion of the adhesive matrix in terms of three dimensional stability.

It will be appreciated that patches of the present invention may comprise components other than adhesive and granisetron. Suitable backings, for example, are described hereinbelow. They may take any suitable form, and may be in the form of films or materials, for example. Films may be selected for breathability and/or their occlusive properties. It is possible to use metallised films, but it is generally preferred to use plastics, such as polyethylene terephthalate (PET). Materials may be selected from woven and non-woven, with non-wovens generally providing a greater degree of flexibility. Such materials are generally highly porous, and it is preferred to impregnate them with a drug-proofing substance and, optionally, a water-proofing substance, as well known in the art.

The adhesive is generally provided as a layer which is preferably laminated directly onto the backing, although the backing itself may be multilaminate. The adhesive is suitable to directly adhere to most backings, but it may be necessary, or desirable, in some instances, to provide further means for the adhesive to be secured to the backing, such as by a cross-linking layer.

While it is generally not preferred or necessary to incorporate other ingredients in the adhesives of the present invention, it will be appreciated extra formulants may be added as desired and that certain formulations or conditions may benefit from other ingredients. For example, the addition of vegetable oils may be

used to further enhance early release, suitable examples including coconut oil and groundnut oil. Such other ingredients as softeners and tackifiers may also be included, but it is generally preferred to minimise such ingredients.

Patches of the present invention are also useful in the treatment of emesis associated with fractionated chemotherapy. Fractionated chemotherapy regimens involve administering chemotherapy on successive days at reduced daily rates, which is intended to reduce side effects and increase efficacy. Unfortunately, the side effects associated with fractionated chemotherapy still include substantial nausea and vomiting and therefore 5-HT₃ antagonists, including granisetron, are also utilised in these treatment regimens. Fractionated chemotherapy is usually given over a five day period (although this can vary) and the associated symptoms of nausea and vomiting are prevented by daily doses of anti-emetics – in the case of granisetron this is generally 2mg per day. Hence, the pattern of administration is similar to that for the prevention of the acute and delayed emesis associated with single dose chemotherapy. Patches to protect against the nausea and vomiting associated with fractionated chemotherapy may be suitably constructed to deliver consistently higher levels of drug than one for the treatment of single dose chemotherapy, and this is readily achieved by manipulation of the patch area and loading dose.

Patches of the invention may also be used in the treatment and prophylaxis of postoperative nausea and vomiting (PONV). It will be appreciated that, where used herein, treatment includes prophylaxis, where appropriate. PONV remains a frequent and unpleasant experience for patients undergoing surgery. On average, 20 to 30 percent of surgical subjects suffer from PONV symptoms, depending on individual subject factors, type and duration of anaesthesia and type of surgery. PONV can result in dehydration, electrolyte imbalances, prolongation of stay in the recovery room, unanticipated hospital admissions and loss of work. As with the treatment of chemotherapy induced nausea and vomiting, addition of dexamethasone to the regimen improves the efficacy of the regimen.

The usual regimens to prevent post-operative nausea and vomiting are single administrations of 5HT₃ antagonists, immediately pre- or post surgery. Such doses may be replaced by a transdermal patch applied prior to surgery, in light of recent

advances in the understanding of reductions possible in the required dose of granisetron for the prevention of post-operative nausea and vomiting. In one study, clinical data suggested granisetron was effective in the prevention of post-operative nausea and vomiting at doses as low as 0.1 mg, such doses be readily dispensable by patches of the invention.

Other indications are as indicated above, and include the treatment and prophylaxis of fibromyalgia and pain associated therewith, migraine, anxiety, cognitive and psychotic disorders, depression, schizophrenia, psychosis in postnatal depression, irritable bowel syndrome, alcoholism, obstructive sleep disturbed breathing, motion sickness, loss of cognitive function such as Alzheimer's, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation, eating disorders, obsessive compulsive disorder, gastric motility disorders (diarrhoea), dyspepsia and cocaine dependence.

EXAMPLE 1

To examine the possibility of incorporating granisetron into adhesives that contain nucleophilic monomers, the drug was formulated into four different National Starch adhesives. As listed in Table 1, one of these adhesives contained polymers with no functionality, two contained polymers with acidic functionality and the fourth hydroxyl functionality.

Table 1

Adhesive	Chemical composition	Functional groups	~% Functional Monomer
DT 4098	Acrylate-vinylacrylate	None	0
DT 2052	Acrylate-vinylacrylate	COOH	5
DT 2353	Acrylate	COOH	5
DT 2287	Acrylate-vinylacrylate	OH	5

“~% Functional Monomer” indicates the approximate level of acidic or OH containing monomer (w/w) used in preparation of the adhesive, within a 10% tolerance.

Accompanying Figure 1 depicts the *in vitro* murine skin permeation ($\mu\text{g}/\text{cm}^2$) of granisetron from 3% formulations of granisetron in the adhesives listed in Table 1. Each of these formulations was produced at a coating weight of $85 \text{ g}/\text{m}^2$ to give a drug loading of approximately $260 \mu\text{g}/\text{cm}^2$. Crystallisation was not observed in any of the devices manufactured.

Table 2 shows the levels of permeation from the various formulations at various time intervals, and shows levels of flux from DT 2287 30x greater than those obtained with the non-nucleophilic and electroneutral DT 4098. The reason for the convergence at higher levels is owing to the depletion of drug from the adhesive in DT 2287.

Table 2

Adhesive	Functional groups	Permeation ($\mu\text{g}/\text{cm}^2$)					
		3	6	12	24	36	48
DT 4098	None	1	2.9	13.4	48.5	n/s	129.8
DT 2052	COOH	0.8	2.3	16.1	15.9	24.8	33.3
DT 2353	COOH	0.3	0.8	1.7	3.7	5.4	7.2
DT 2287	OH	31.7	92.0	170.8	256.6	282.4	290.4

Permeation from the adhesives containing acidic moieties was very much lower than that from the adhesive with no functionality.

Table 3 shows the same data as in Table 2, but treated so as to show average flux.

Table 3

Adhesive	Functional groups	Average flux ($\mu\text{g}/\text{cm}^2/\text{hr}$)					
		3	6	12	24	36	48

DT 4098	None	0.33	0.48	1.1	2.0	-	2.7
DT 2052	COOH	0.27	0.38	1.3	0.66	0.69	0.69
DT 2353	COOH	0.10	0.13	0.14	0.15	0.15	0.15
DT 2287	OH	10.6	15.3	14.2	10.7	7.8	6.05

Table 4 shows the same data, but treated to show absolute flux, which is the taken as the gradient at the time point selected, and further highlights the superiority of the patches of the invention over the initial six hours. Patches with substantially higher loading could be expected to deliver higher doses for longer.

Table 4

Adhesive	Functional groups	Absolute flux ($\mu\text{g}/\text{cm}^2/\text{hr}$)					
		3	6	12	24	36	48
DT 4098	None	0.33	0.63	1.8	2.9	-	3.3
DT 2052	COOH	0.27	0.50	2.3	-	0.74	0.71
DT 2353	COOH	0.10	0.17	0.15	0.17	0.15	0.15
DT 2287	OH	10.6	20.1	13.1	7.2	2.2	0.67

A surprisingly high degree of granisetron permeation from the adhesive containing hydroxyl groups was observed (Figure 1). The flux from this formulation was sufficiently high to deplete the device of granisetron after only 24 hours (as indicated by the plateauing of the permeation curve for the DT 2287 formulation in Figure 1). This complete depletion indicates that it is very unlikely that any lasting interaction occurred between the drug and this adhesive. The relative depletion, in terms of %, of the formulations examined over a 24 hour period is depicted in Figure 2 and clearly shows the surprising efficiency of the DT 2287 formulation.

EXAMPLE 2

Drug stability in the best formulation of Example 1 was investigated.

Stability data for the patches formulated in DT 2287 and stored at three temperatures for six weeks are shown in Table 5. There was no observed decrease in granisetron content of the patches indicating that, even under accelerated conditions at 40°C, the drug is stable in these devices.

Table 5
Stability of granisetron patches

Storage temperature	Storage period	% Granisetron
40°C	6 weeks	99.3
25°C	6 weeks	99.4
5°C	6 weeks	99.4
Standard		99.5

Figure 3 depicts the results of an *in vitro* human skin permeation study conducted using an 8% granisetron formulation coated at a weight of 110g/m². This equates to a granisetron loading of about 880 µg/cm². After 96 hours the total permeation amounted to approximately 600 µg/cm² which equates to about 70% of the patch loading. Although permeation is plateauing after 96 hours, it is assumed that the patch would continue to deliver drug for another 24 hours.

Figure 4 is a plot of the gradient of Figure 1 against time *i.e.* a depiction of flux against time. This flux profile was modelled and used as an input for a simple pharmacokinetic model (based on PK data from patients) to predict the *in vivo* performance of a 10cm² patch as shown in Figure 5.

The data in Figure 3 are indicative that the formulation will deliver drug over several days and is suitable for a five day period, such as that over which granisetron is frequently prescribed. Figure 3 also shows the predicted effect of applying the transdermal patch at different times *i.e.* prior to chemotherapy, and demonstrates how such a device may be utilised in practice to protect against acute and delayed emesis as well as emesis associated with fractionated chemotherapy.

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Claims:

1. An adhesive patch suitable for the transdermal administration of granisetron, wherein the adhesive is an acrylic adhesive containing non-acidic hydroxyl moieties.

ABSTRACT**TRANSDERMAL GRANISETRON**

Adhesive patches for the transdermal administration of granisetron, comprise an acrylic adhesive containing non-acidic nucleophilic moieties which substantially increase flux of granisetron across the skin.

Figure 1

In vitro murine skin permeation ($\mu\text{g}/\text{cm}^2$) of granisetron from formulations of different adhesive polymer functionality

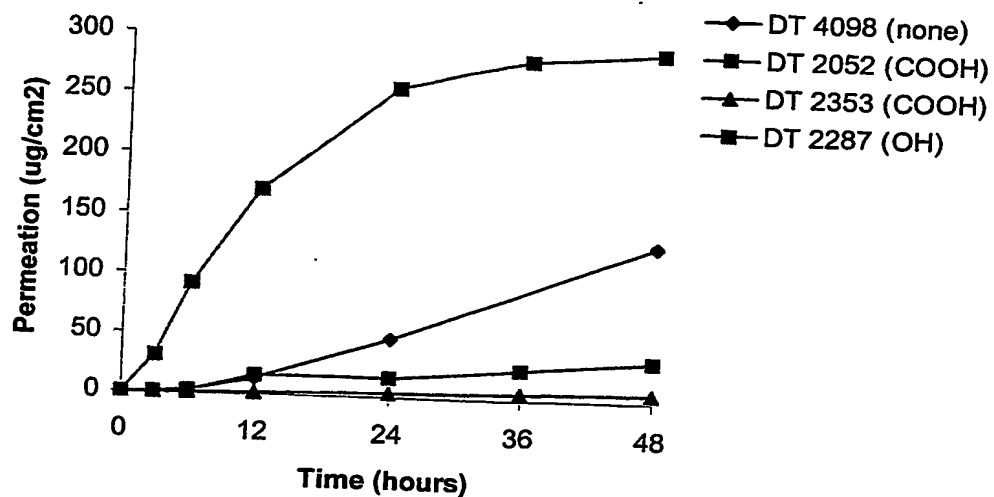


Figure 2

In vitro murine skin permeation (% of applied dose) of granisetron from formulations of different adhesive polymer functionality

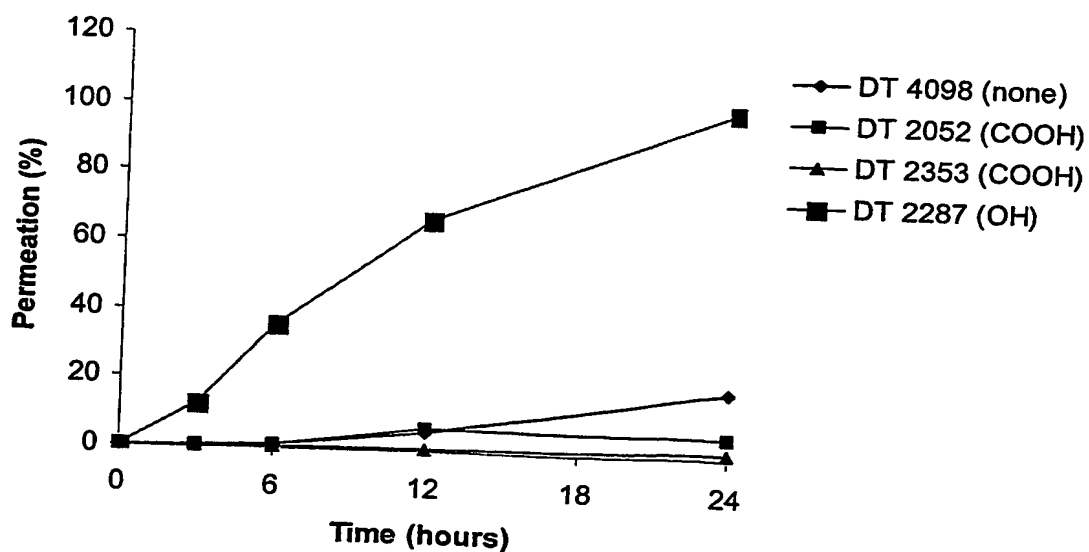


Figure 3

In vitro human skin permeation of granisetron from DT 387-2287 adhesive (n=4)

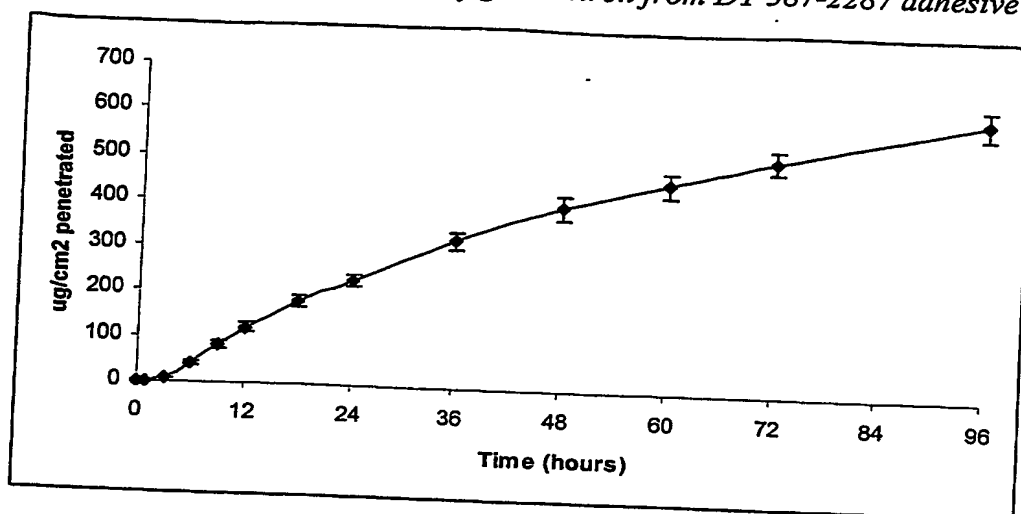


Figure 4

Experimental and modelled in vitro human skin permeation of granisetron from DT 2287 adhesive ($\mu\text{g}/\text{cm}^2/\text{hr}$)

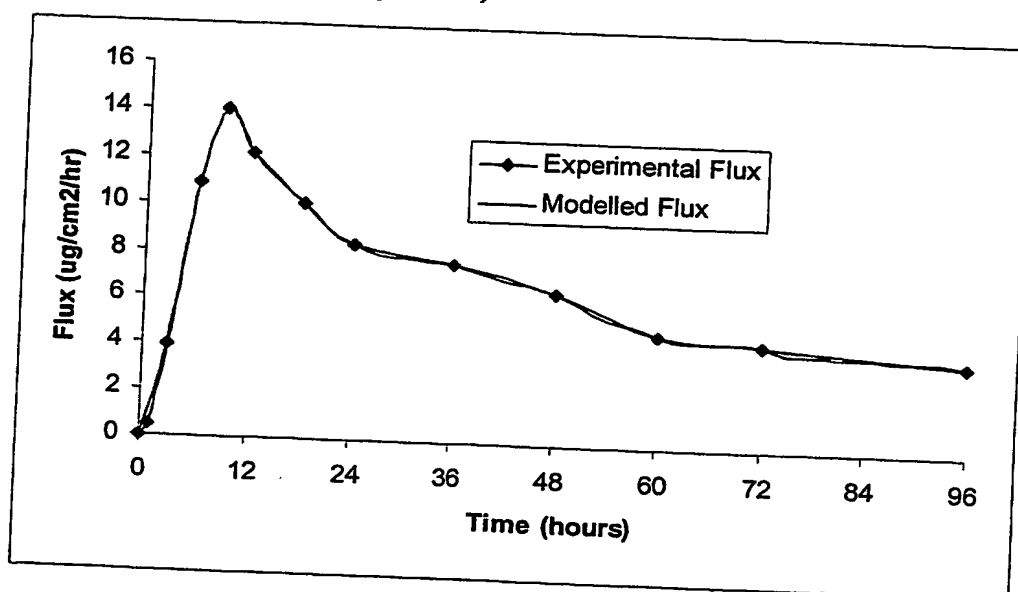


Figure 5

Simulated granisetron plasma profiles from a 10cm² patch compared with experimental plasma profile at steady-state after repeated oral administration of 1 mg granisetron in patients

